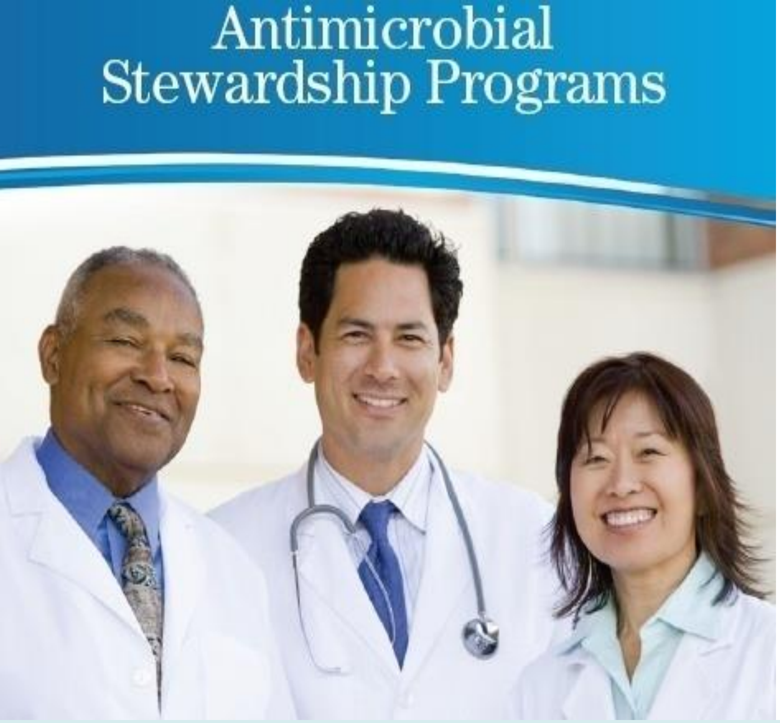



# Antimicrobial Stewardship:

## Arizona Partnerships Working to Improve the Use of Antimicrobials in the Hospital and Community

## Part 9

**"Antibacterials – indeed, anti-infectives as a whole – are unique in that misuse of these agents can have a negative effect on society at large. Misuse of antibacterials has led to the development of bacterial resistance, whereas misuse of a cardiovascular drug harms only the one patient, not causing a societal consequence."**

**- Glenn Tillotson; Clin Infect Dis. 2010;51:752**

**"…we hold closely the principles that antibiotics are a gift to us from prior generations and that we have a moral obligation to ensure that this global treasure is available for our children and future generations."**

**- David Gilbert, et al (and the Infectious Diseases Society of America). Clin Infect Dis. 2010;51:754-5**

# A Note To Our Readers and Slide Presenters

The objectives of the Subcommittee on Antimicrobial Stewardship Programs are directed at education, presentation, and identification of resources for clinicians to create toolkits of strategies that will assist clinicians with understanding, implementing, measuring, and maintaining antimicrobial stewardship programs.

The slide compendium was developed by the Subcommittee on Antimicrobial Stewardship Programs (ASP) of the Arizona Healthcare-Associated Infection (HAI) Advisory Committee in 2012-2013.

ASP is a multidisciplinary committee representing various healthcare disciplines working to define and provide guidance for establishing and maintaining an antimicrobial stewardship programs within acute care and long-term care institutions and in the community.

Their work was guided by the best available evidence at the time although the subject matter encompassed thousands of references. Accordingly, the Subcommittee selectively used examples from the published literature to provide guidance and evidenced-based criteria regarding antimicrobial stewardship. The slide compendium reflects consensus on criteria which the HAI Advisory Committee deems to represent prudent practice.

# Disclaimers

All scientific and technical material included in the slide compendium applied rigorous scientific standards and peer review by the Subcommittee on Antimicrobial Stewardship Programs to ensure the accuracy and reliability of the data. The Subcommittee reviewed hundreds of published studies for the purposes of defining antimicrobial stewardship for Arizonan clinicians. The Arizona Department of Health Services (ADHS) and members of its subcommittees assume no responsibility for the opinions and interpretations of the data from published studies selected for inclusion in the slide compendium.

ADHS routinely seeks the input of highly qualified peer reviewers on the propriety, accuracy, completeness, and quality (including objectivity, utility, and integrity) of its materials. Although the specific application of peer review throughout the scientific process may vary, the overall goal is to obtain an objective evaluation of scientific information from its fellow scientists, consultants, and Committees.

Please credit ADHS for development of its slides and other tools. Please provide a link to the ADHS website when these material are used.

# Introduction to Slide Section



- **Preface:**

  Developing a schedule for ASP projects depends strongly on the needs of the institution. However, this needs to be balanced against those projects which are simpler ("low-hanging fruit") versus more difficult projects ("high-hanging fruit") which require a greater knowledge of data collection capabilities and data analysis. The latter should be considered once the ASP is well-established and has tackled issues such as IV-to-PO sequential therapy.
- **Content:**

  37 slides with 2 additional slides.
- **Suggestions for Presentation:**

  Identification of projects requires significant time to discuss with the ASP committee, physicians, department heads, and pharmacy. The presentation will require at least 1 hour with another hour of discussion. Planning for the first and following years requires evaluation of all potential projects and incorporation of these into a timeline as well as identifying potential clinical and financial outcomes.
- **Comments:**

  These slides are the real "nuts and bolts" which determine daily activities and support of the ASP's objectives. The slides should be carefully reviewed prior to presentation.

# ANTIMICROBIAL STEWARDSHIP PROJECTS:
# INITIATION AND ADVANCED

# Identify Areas for Improvement: Baseline Data Collection Examples

- What is the prevalence of inappropriate antibiotic use? Examples:
  - Treatment of asymptomatic bacteriuria
  - Dual anaerobe therapy, such as metronidazole prescribed with piperacillin/tazobactam, ampicillin/sulbactam, or carbapenems
  - Broad spectrum antibiotics for infections due to organisms with effective narrower spectrum agents per susceptibility report
- What is the lag time between culture &sensitivity results and effective antibiotic therapy?
- How often are positive blood cultures not covered with appropriate agents in timely manner?
- For patients who are converted to PO antibiotics, what % are converted back to IV?
- Do you have data on % patients who receive antibiotics for > 3days?
- Does the antibiogram eliminate duplicate agents?
- What is the frequency of prescribers stating an antibiotic plan in the chart?
- What is the prescriptive compliance for institutional guidelines regarding use of broad-spectrum antibiotics?
- What is the frequency of non-compliance with TJC/CMS core measures for CAP treatment?

# Identify Areas for Improvement: Possible Projects

- IV-to-PO switch - the most basic stewardship function
- Ensure all antibiotic orders carry an indication
- Improve SCIP performance measures
- Reassess all antibiotic therapies at 72 hours
- There is a daily antibiotic plan, or recognition of current antibiotics
- Improve empiric antibiotic therapy in the ICU patient
  - Early appropriate therapy decreases ICU LOS, costs, and mortality
  - Develop the “ICU antibiogram” or even a “VAP antibiogram”
  - Conduct a retrospective audit on appropriate empiric (<72 hours) therapy
- “Bug-drug mismatch” – get the daily culture report
- Asymptomatic bacteriuria – discourage antibiotic use; educate clinicians
- Sepsis campaign – get cultures before antibiotics are administered if possible
- Check daily blood culture reports for significant pathogen not treated or potential contamination
  - If contamination is highly suspected work towards discontinuation of antibiotics

# Educational Opportunities

- Pharmacy staff
  - Scheduled inservices to reinforce antibiotic use guidelines within the institution (and why!)
  - Includes beta-lactam selection, when to use fluoroquinolones, criteria for IV-to-PO transition therapy, MRSA treatment options, empiric versus targeted therapy, and disease-based reviews (e.g., CAP vs HCAP, candidemia)
- Prescriber education
  - Goal is to maintain collegial relationship while quietly changing prescribing patterns
  - Educational seminars, daily rounds, conferences
  - Develop a toolbook with prescriber input
  - Face-to-face interactions with single prescribers
  - Don't forget NPs and PAs

# Educational Opportunities (cont'd)

- Nursing
  - Appropriate reasons for cultures (e.g. urine cultures in patients with catheters, no chronic wound swabs)
- Microbiology
  - Antibiogram templates which may improve prescriber education
  - Consider combined ID-microbiology rounds (works well in academic centers with ID fellows)
  - Feedback on patient outcomes related to reporting susceptibilities and rapid testing diagnostics
- Infection prevention
  - Relate epidemiology and patient tracking with antimicrobial prescribing
  - Turnaround time between prescriber alerts (issued by laboratory) and isolation (if appropriate) and therapy – work with laboratory and computer systems

# Example: Providing Usage Feedback to Prescribers is Education to Improve Antimicrobial Use

- 110-bed VA facility
- 2,807 antibiotic courses evaluated for compliance with institutional guidelines
- Compared to historical controls (prior to ASP audit and feedback)
- ASP recommendations were made direct-to-prescriber in several categories:
  - Unjustified use of an antimicrobial
  - Inappropriate dose
  - Availability of a more effective drug
  - Availability of a less toxic drug
  - Availability of a drug with narrower spectrum
  - Switch from IV to PO therapy
  - Duration of therapy can be shortened
- Audits were performed with feedback and consisted of the following:
  - Weekly reports on compliance with guidelines and ASP recommendation acceptance (internal medicine, surgery)
  - Quarterly department-specific reports (department heads, P&T, infection control, CQI)
  - Monthly reports on ID topics

Arnold F et al. Infect Control Hosp Epidemiol. 2006;27(4):378-82

# Framework for Studying Disease States: Looking for Improvements in Outcomes

| Intervention | Application to Skin and Soft Tissue Infection |
|---|---|
| Baseline assessment | • Retrospective audit of specific SSTI (cellulitis, surgical site infection, abscess, etc)<br>• What needs improvement – meet with IDs |
| Identify specific and measurable outcomes | • What information needs to be collected?<br>• Resources – IT, pharmacy computer, CDSS |
| Involve key stakeholders | • Internal med, hospitalist, ED, ID, CMO, surgery |
| Design the intervention with team input | • Current state of practice versus what needs to be achieved<br>• How to get there with the intervention |
| Implement a new multi-faceted approach to disease state | • Guideline development and presentation to P&T<br>• Education of stakeholders and department heads |
| Evaluate interim results, such as safety and effectiveness of new approach | • Prospective; collect data over shorter period<br>• Interim study post-intervention – what has been achieved<br>• Reports |
| Modify the intervention as needed | • Revise guidelines, as needed<br>• P&T, re-educate; highlight changes |

# Don't Forget Stewardship Opportunities with Treatment of Fungal Infections

Low-Hanging Fruit

- Formulary echinocandin choice; therapeutic interchange opportunities
- IV-to-PO conversion of fluconazole
- IV-to-PO conversion of voriconazole
- Ensure acidic gastric environment for absorption of some agents
- Switch to fluconazole from other anti-fungals for *Candida albicans*, as appropriate
  - Identification of *C.albicans*
  - Rapid identification, e.g., PNA-FSH
- Susceptibilities of *C.albicans* and selected non-albicans *Candida spp*
- Comprehensive care bundle on the management of candidemia
  - Compliance with candidemia care bundle was significantly higher in the AST group versus the control group (78.0% vs 40.5%, p=0.0016); significantly improved rates of ophthalmologic examination (97.6% vs 75.7%, p=0.0108), selection of appropriate antifungal therapy (100% vs 86.5%, p=0.0488), and compliance with appropriate therapy duration (97.6% vs 67.7%, p=0.0012)[1]
- Therapeutic drug monitoring, i.e., voriconazole and posaconazole, due to PK variability, variable absorption (food and gastric pH effects)

High-Hanging Fruit

1 Antworth A et al. Pharmacotherapy. 2013;33(2):137-43.

# ANTIMICROBIAL STEWARDSHIP PROJECTS:

# LOW-HANGING FRUIT

# Drug Optimization Program: IV-to-PO and Dosing

- All patients who receive targeted IV and PO antibiotics are monitored for opportunities to change the route or dose depending upon the clinical picture
- Optimization can be protocol-driven but requires sound clinical judgment
- Monitoring patient responses avoids the single observation point in time
  - How many patients converted from IV to PO agent are changed back to the IV antibiotic within 72 hours? (Report these results with outcomes analysis)
- Correction of under-dosed regimens (as important as over-dosed regimens)
  - Do patients need increased dosing? Example: MSSA bacteremia in a patient on nafcillin 2 grams IV Q8H
- Pharmacodynamic modeling considers site of infection, pathogen-specific MIC, and looks for opportunity to employ prolonged/extended infusions
  - Loading doses in obesity and high volume of distribution
  - Rapid clearance due to sepsis
  - Dosing in special disease states: CHF, cystic fibrosis, cirrhosis, burn patients
- Renal dose adjustments of renally-cleared antimicrobials

# Example: IV-to-PO Conversion Form and Criteria

**IV to PO Conversion Order Form/Worksheet**

Height: ___________ Weight: _____________

Allergies: ________________________________

(Addressograph)

**The Pharmacy & Therapeutics Committee has approved that patient's meeting the following criteria can automatically be converted to a PO version of the listed medication.**

**Date/Time:** ____________

Pharmacy recommends:

D/C (enter drug,dose, and route)

Start (enter drug,dose, and route)

**This change will take place on** _______ **at** _______

Pharmacist's signature:

______________________________

**Criteria for Conversion to PO:**

_____ Tolerating other drugs by oral route

_____ Being fed enterally (at minimum a clear liquid diet), i.e. a functioning GIT

_____ Patient does NOT have persistent N/V, ileus, gastric outlet obstruction, active GI bleed, loss of consciousness, NPO orders that applies to all meds

If an antibiotic: (**in addition to above**)

_____ Resolution of fever for 24 hours

_____ CBC improving, preferably < 15K in absence of steroids

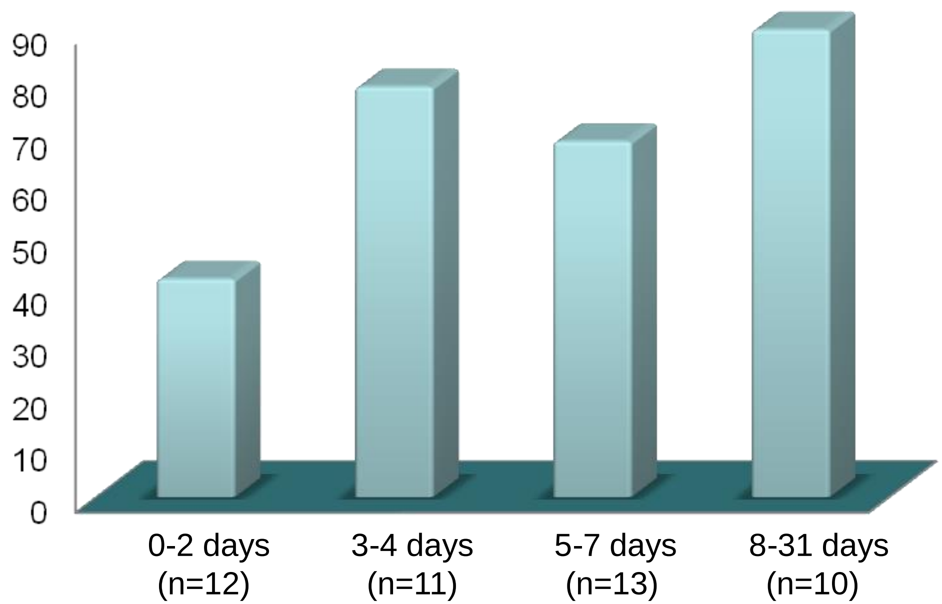
_____ Patient does NOT have meningitis, endocarditis, septicemia, neutropenia, osteomyelitis, or MRSA

_____ Hemodynamically stable

# Example: Package Labeling, RN Education, and Timing of Administration

- Co-administration of an oral fluoroquinolone with divalent/trivalent cation-containing (DTCC) compounds inhibits fluoroquinolone (FQ) absorption
- Case-control study with 46 inpatients (receiving an oral FQ and a DTCC within 2 hours)
- Patients with a resistant isolate had been exposed to nearly twice as many days of fluoroquinolone-DTCCs co-administration (P=0.04).
- Efforts should be directed at modifying hospital policies for dosing oral fluoroquinolones and DTCCs to prevent co-administration

**% Subjects with Fluoroquinolone-Resistant Isolates**




**Days of Coadministration (in quartiles)**

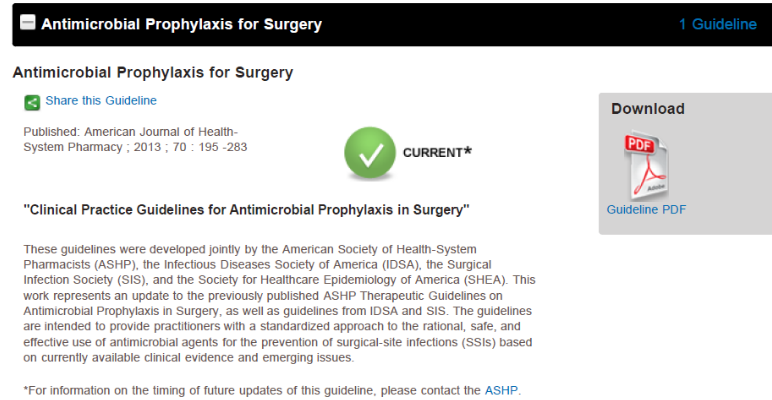
Adapted from: Quain R et al. *Int J Antimicrob Agents* 2005;26:327-30.

# Example:  A Simple Community-Acquired Pneumonia (CAP) Audit

- 17 agents used to treat 176 unique episodes of CAP
- 96 patients received 3 or more antibiotics
- Included several cases of use of piperacillin-tazobactam, cefotetan, fluconazole, and carbapenems for at least 3 days
- 21 cases were treated with cefazolin (no patient had concomitant SSTIs)
- No positive culture results for *Pseudomonas aeruginosa*
- All but 5 patients had at least one blood culture performed within 24 hours of admission
- Potential questions to optimize treatment of CAP:
  - Number and costs of antibiotics consistent with core measures and IDSA guidelines?
  - What are drug and total costs associated with these admissions?
  - What was the range, mean, and median length of stay for these patients?
- Business model calculations:
  - Cost differences between audited antibiotics versus compliance with guidelines?
  - What cost- savings for appropriate blood cultures and decreased LOS by 1 day?
  - If ADRs to inappropriate antibiotics, could these have been prevented?

Adapted from:  MUE/DUE CAP, 1995; courtesy Mark Redell

# Perioperative Antibiotic Prophylaxis: Interventions and SCIP 2013




- Goals
  - Minimize surgical site infection (SSI) rates
  - Decrease variability
  - Compliance with SCIP measures
  - Follow national guidelines and best practices
  - Consider local epidemiology
- Surgical Care Improvement Project (SCIP) [1]
  - SCIP-Inf-1: Prophylactic antibiotic received within 1 hr prior to surgical incision (2 hrs for vancomycin)
  - SCIP-Inf-2: Prophylactic antibiotic selection for surgical patients according to procedure type
  - SCIP-Inf-3: Prophylactic antibiotics discontinued within 24 hours after surgery end time (48 hours for cardiac)
- Opportunities for antibiotic stewardship include education on recently published guidelines[2]; changes from previous recommendations

1 SCIP guidelines are available at: http://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx
2 Bratzler D et al. Am J Health-Syst Pharmacy. 2013;70:195-283.

# Examples of ASP Projects Involving SCIP Measures

| **Project Addressing Specific Performance** | **Reason to Optimize Performance** | **Examples** |
|---|---|---|
| **Drug selection/dosing**<br>• Based on type surgical procedure<br>•Weight-adjusted dosing | • Decrease SSI rate | • Order forms |
| **Duration**<br>• < 24 hours for most procedures<br>• Historical acceptance for 48 hours in CV surgery | • Lack of evidence to show durations > 24-48 hours decreases SSI<br>• Emergence /selection of resistance | •Order forms with automatic stop orders |
| **Education**<br>• Written material<br>• Inservices to nursing, anesthesiology | • Compliance with guidelines; regulatory | • Post OR guidelines, SCIP measures<br>• Outpatient surgery antibiotic prophylaxis order form |
| **Special circumstances**<br>• Re-dosing for prolonged procedures | • Increased SSI rate | • Audible and visual automated reminder systems |

Bratzler D et al. Am J Health-Syst Pharmacy. 2013;70:195-283.

# ANTIMICROBIAL STEWARDSHIP PROJECTS:

# HIGH-HANGING FRUIT AND TAKING YOUR PROGRAM TO THE NEXT LEVEL

# Examples of Higher-hanging Fruit: Optimizing Antibiotic Selection

- In suspected or proven HCAP, vancomycin was discontinued in 88 of 91 patients with negative nasal and throat swabs for MRSA when adequate lower respiratory tract cultures were not available and clinical pulmonary infection scores were <6[1]
- Large urban multi-campus academic medical center addressed appropriate antibiotic selection in the ED (2008 to 2011; quasi-experimental before-after study)[2]
  - Interventions:  algorithm for antibiotic selection, “CAP Kit”, and pre-loading an automated ED medication dispensing and management system
  - Appropriate antibiotic selection increased from 55% to 65% to >90% in 2 Eds (P=0.004)

1  Boyce J et al. Antimicrob Agents Chemother. 2013;57(3):1163-8.
2  Ostrowsky B et al. Infect Control Hosp Epidemiol. 2013;34(6):566-72.

# Optimizing Patient Outcomes in Ventilator-associated pneumonia (VAP): Use of a Clinical Pathway to Improve Empiric Antibiotic Therapy

- Appropriate antibiotic therapy improved (71.6% vs 48.6%; P=0.007)
- Infection-related mortality was reduced by 69% (8.5% vs 21.6%; P=0.029)
- Mean infection-related length-of-stay decreased (11.7 ±8.1 vs 26.1±18.5; P<0.001)
- Fewer superinfections overall and by MDR pathogens
- A number of patients with nonsusceptible *P.aeruginosa* were successfully treated

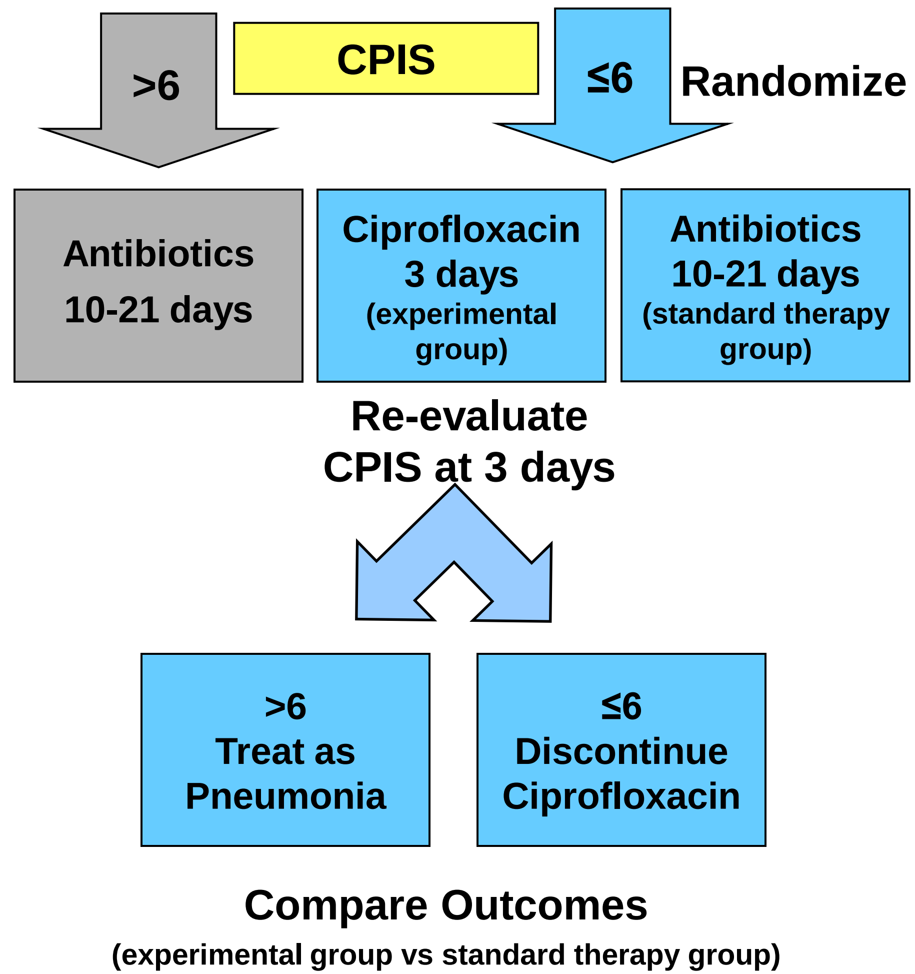
| Measurement | Historical control group (n=73) | Clinical pathway group (n=93) | P Value |
|---|---|---|---|
| COST VAP ($) | | | < 0.001 |
| Mean ± SD | 95,150 ± 84,260 | 44,435 ± 29,995 | |
| Median (IQR) | 75,698 (38,449 – 137,922) | 35,841 (22,288 – 56,351) | |
| Range | 11,465 – 635,963 | 10,252 – 153,685 | |
| COST POSTVAP ($) | | | 0.077 |
| Mean ± SD | 108,955 ± 88,842 | 85,730 ± 55,437 | |
| Median (IQR) | 95,479 (47,979 – 156,556) | 76,443 (41,640 – 115,010) | |
| Range | 11,465 – 635,963 | 10,334 – 283,332 | |
| Antibiotic cost ($) | | | 0.450 |
| Mean ± SD | 934 ± 1533 | 766 ± 755 | |
| Median (IQR) | 482 (222 – 985) | 535 (261 – 998) | |
| Range | 12 – 10,572 | 85 – 5,125 | |


1 Nicasio A et al. J Crit Care. 2010;25:69-77
2 Nicasio A et al. Pharmacother. 2010;30:453-62

# Stewardship Based on Infection Severity Score: Decreased Antibiotic Duration and Patient-Level Resistance

| Variable | Experimental Group (n=39) | Standard Therapy Group (n=42) |
|---|---|---|
| Antibiotic continuation > 3 days | 28% (11/39) | 97% (38/39) |
| Duration of antibiotics, days, mean (range) | 3 (3) | 9.8 (4-20) |
| Total antibiotic costs (mean/pt) | $6,482 ($259) | $16,004 ($640) |
| Length of ICU stay, days (mean/median) | 9.4 / 4 | 14.7 / 9 |
| Antimicrobial resistance and/or superinfections | 14% (5/37)<br>0 | 38% (14/37)<br>9.8 (4-20) |

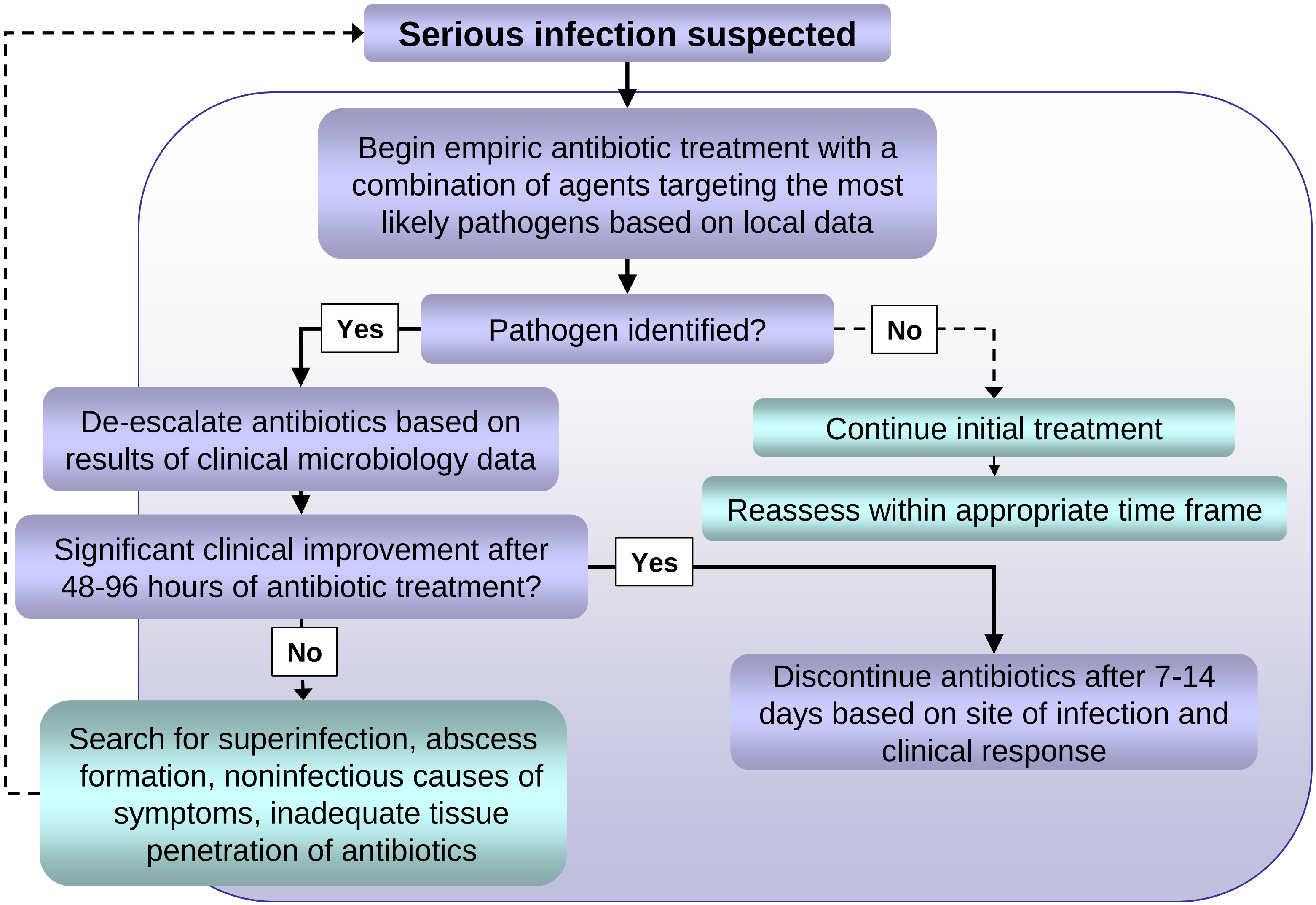
**Study was terminated early because attending physicians began to treat standard care group with 3 days of therapy**




CPIS = clinical pulmonary infection score (temperature, peripheral WBC count, tracheal secretions, oxygenation, progression of pulmonary infiltrate, culture of tracheal aspirate; score >6 is suggestive of pneumonia


Singh N et al. Am J Respir Crit Care Med. 2000;162:505-511

# De-escalation: Streamlining Therapy to Narrowest Spectrum Agent Based on Culture Results




ATS-IDSA Guidelines. *Am J Respir Crit Care Med*. 2005;171:388-416

# Escalation and De-Escalation Patterns in the Treatment of VAP (n=390 patients)

| Number of Drugs \ Spectrum of Activity | *Decrease* | *No change* | *Increase* |
|---|---|---|---|
| *Increase* | **3** | **13** | **12** |
| *No change* | **15** | **242** | **19** |
| *Decrease* | **39** | **34** | **17** |

**De-Escalation** (22%)

**No Net Change** (67%)

**Escalation** (11%)

Kollef MH, et al. *CHEST* 2006;129:1210-8

# Evaluate Antibiotic Combinations to Reduce Redundant Therapy

- Rationale
  - Beyond "getting it right" empiric coverage, lack of evidence for the most part
  - May increase the probability of AEs and/or resistance and increase cost
- Pharmacist-based intervention at a 600-bed public teaching hospital[1]
  - Screening of 1,189 inpatients receiving $\geq$2 antibiotics during a 23-day surveillance via computer-assisted tool
  - 192 episodes with 137 (71%) deemed inappropriate combinations
  - MD errors in prescribing in 77/137 episodes, primarily redundant coverage for gram-positive or anaerobic organisms
  - Changing regimens decreased 584 days of therapy of redundant drug
  - Clinical and microbiologic outcomes with monotherapy were significantly better than with combination and associated with less AEs
  - Cost savings realized despite the cost of a pharmacist
  - No benefit seen in combination therapy for *P aeruginosa*[2]

1 Glowacki RC et al. *Clin Infect Dis* 2003;37:59-64.
2 Paul M, et al. *BMJ* 2004;328:668.

# Evaluate Antibiotic Therapy at Defined Time Periods for Stewardship Opportunity: Example in the ICU

- Prospective, controlled interrupted time series in a single tertiary care center with 3 intensive care units
- Formal review of all critical care patients on their third or tenth day of broad-spectrum antibiotic therapy was conducted, and suggestions for antimicrobial optimization were communicated to the critical care team
- Results
  - The mean monthly broad-spectrum antibiotic use decreased from 644 days of therapy per 1,000 patient-days in the pre-intervention period to 503 days of therapy per 1,000 patient-days in the post-intervention period ($P<0.0001$)
  - The incidence of nosocomial *C. difficile* infections decreased from 11 to 6 cases in the study intensive care units, whereas the incidence increased from 87 to 116 cases in the control wards ($P=0.04$)
  - Overall gram-negative susceptibility to meropenem increased in the critical care units
  - ICU length of stay and mortality did not change
- Institution of a formal prospective audit and feedback program appears to be a safe and effective means to improve broad-spectrum antimicrobial use in critical care

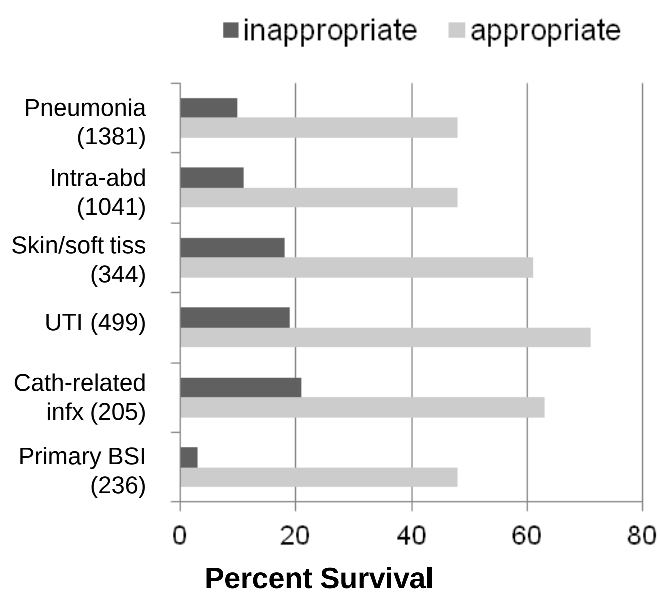
Elligsen M et al. Infect Control Hosp Epidemiol. 2012;33(4):354-61

# Severe Sepsis/Septic Shock: The Value of Appropriate Antibiotics

- The survival rates after appropriate and inappropriate initial antimicrobial therapy were 52.0% and 10.3%, respectively (OR, 9.45; 95% CI 7.74 to 11.54, $p<0.0001$)
- The association remained robust following adjustment for many clinical factors

- There was a significant association at the <1 hr time point for mortality with early goal-directed therapy (EGDT) which included appropriate antibiotics
- Study provides both a severe sepsis pathway and a severe sepsis antibiogram

1

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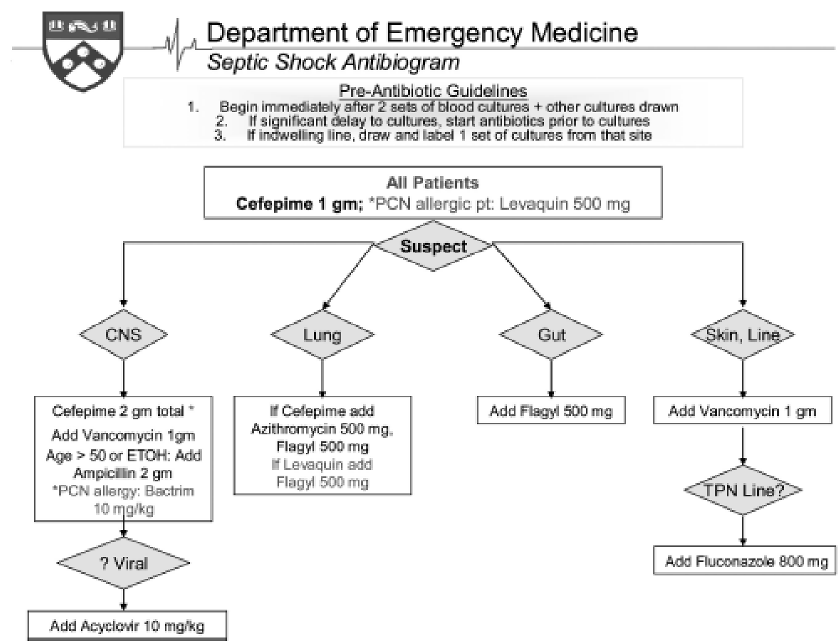




1 Kumar A et al. CHEST. 2009;136:1237-48
2 Gaieski D et al. Crit Care Med. 2010;38:1045-53

# Shorter Antibiotic Courses Matter

- Goals of reducing antibiotic durations of therapy[1]:
  - Decreased selection of resistant pathogens
  - Decreased *Clostridium difficile* infection
  - Decreased antibiotic-related organ toxicity
  - Decreased hospital costs
  - Improved compliance with outpatient antibiotic regimens
  - Potential earlier removal of an IV catheter

- How were current treatment durations determined?
  - Trial and error
  - Well-defined endpoints, e.g., mortality, persistent bacteremia, recurrence
  - Historical data, often very old, which established early “standards”
  - Limited or absent randomized clinical trials – mostly observational studies, clinical experience, and expert opinion
  - Lack of perceived harm with longer courses

1 File T. J Hosp Med. 2012 (suppl);7:S22-S33.

# Guidelines Support Treatment of Many Infections With Shorter Courses of Therapy: CAP/HAP

- Community-acquired pneumonia (CAP), adults[1,2]
  - Patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy
  - Longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis
  - In infants and children >3 months of age, while treatment courses of 10 days have been best studied, shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis
- Hospital-acquired, healthcare-associated, and ventilator-associated pneumonia in adults[3]
  - A shorter duration of antibiotic therapy (7 to 8 days) is recommended for patients with uncomplicated HAP, VAP, or HCAP who have received initially appropriate therapy and have had a good clinical response, with no evidence of infection with non-fermenting gram-negative bacilli

1 Mandell L et al. IDSA-ATS Guidelines on adult CAP. Clin Infect Dis. 2007;44(suppl):S27-S72.
2 Bradley J et al. PIDS-IDSA Guidelines on CAP in infants and children. Clin Infect Dis. 2011;53:617.
3 ATS/IDSA. Am J Respir Crit Care Med. 2005;171:388-416.

# Short-Course (SC) versus Extended-Course (EC) Therapy for Mild-to-Moderate CAP

- Systematically review randomized controlled trials comparing SC (≤ 7 days) and EC (> 7 days) antibiotic regimens for mild-to-moderate CAP
  - 15 randomized clinical studies of monotherapy; 2,796 patients
  - 4 drug classes – FQs, beta-lactams, macrolides, ketolides
- Findings:
  - Overall, there was no difference in the risk of clinical failure between the SC and EC regimens (0.89, 95% CI, 0.78-1.02)
  - There were no differences in the risk of mortality (0.81, 95% CI, 0.46-1.43) or bacteriologic eradication (1.11, 95% CI, 0.76-1.62)
  - In subgroup analyses, there was a trend toward favorable clinical efficacy for the SC regimens in all antibiotic classes (range of relative risk, 0.88-0.94)

Li J, et al. Amer J Med. 2007;120:783-90

# Duration of Therapy in VAP: 8 Days versus 15 Days

- Largest trial to compare outcomes of appropriate initial antibiotic therapy with short-course (8-day; n=197) versus standard course (15-day; n=204) regimens in a well-defined group of ICU patients with quantitatively-confirmed VAP
- Outcomes of 8-day versus 15-day, measured 28 days after VAP onset
  - No excess mortality (18.8% vs 17.2%; 90% CI -3.7% to + 6.9%)
  - No increase in recurrent infections (28.9% vs 26.0%, 90% CI -3.2 to +9.1%)
  - On day 60, no difference in mechanical ventilation-free days, organ failure-free days, length of ICU stay, or mortality rates
  - Higher pulmonary infection-recurrence rate in 8-day group (40.6% vs 25.4%, 90% CI 3.9% - 26.6%) for <u>gram-negative non-fermenting bacilli</u>
  - MDR pathogens emerged less frequently in the 8-day group patients who had recurrent infection (42.1% vs 62.0%; p=0.04)

**If the patient responds rapidly, and the isolated pathogen is susceptible to the initial regimen, therapy may be halted early (7-10 days)**

Chastre J et al. *J AMA* 2003;290:2588-98

# Guidelines Support Treatment of Many Infections With Shorter Courses of Therapy: UTIs

- Diagnosis and treatment of asymptomatic bacteriuria in adults[1]
  - Treat with appropriate antimicrobials: pregnancy (x3-7d); prior to TURP or other urologic procedures associated with bleeding; asymptomatic women with catheter-associated bacteriuria that persists 48hrs after indwelling catheter removal (optional); possibly other conditions, such as neutropenia and post-renal transplant
- Antimicrobial treatment of acute uncomplicated cystitis and pyelonephritis in women[2]
  - Uncomplicated cystitis: nitrofurantoin (100mg BID) x 5d; TMP/SMX (1DS BID) x 3d; fosfomycin (3gm once); or FQ x 3d; beta-lactams x 7d
  - Pyelonephritis: ciprofloxacin (500mg BID or 1gm ER QD) x 7d; aminoglycoside (preceded by optional ceftriaxone 1gm IV/IM x 1) x 7d total; TMP/SMX (1 DS BID) x 14d; or levofloxacin (750mg QD) x 5d

TMP/SMX = trimethoprim/sulfamethoxazole; DS = double-strength tab, 160mg/800mg; FQ = fluoroquinolone

1 Nicolle L et al. IDSA. Clin Infect Dis. 2005;40:643-54.
2 Gupta K et al. IDSA/ESCMID. Clin Infect Dis. 2011;52(5):e103-e120Dis. 2010;50:625-63.

# Guidelines Support Treatment of Many Infections With Shorter Courses of Therapy: UTIs (cont'd)

- Diagnosis, prevention, and treatment of catheter-associated UTIs in adults[1]
  - Provides recommendations when not to use antimicrobials, such as prophylaxis
  - Treatment x 7d for patients with CA-UTI who have prompt resolution of symptoms, and 10-14d of treatment for those with a delayed response, regardless of whether the patient remains catheterized or not; levofloxacin x 5d may be considered in patients with CA-UTI who are not severely ill
  - A 3d antimicrobial regimen may be considered for women ≤65 yrs who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed

1 Hooton T et al. IDSA. Clin Infect Dis. 2010;50:625-63.

# Guidelines Support Treatment of Many Infections With Shorter Courses of Therapy: IAIs

- Complicated intra-abdominal infections (IAIs) in adults[1]
  - Antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control
  - For acute stomach and proximal jejunum perforations, in the absence of acid-reducing therapy or malignancy and when source control is achieved within 24 h, prophylactic antibiotic therapy directed at aerobic gram-positive cocci for 24h is adequate
  - Bowel injuries attributable to penetrating, blunt, or iatrogenic trauma that are repaired within 12 h and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for 24h
  - Acute appendicitis without evidence of perforation, abscess, or local peritonitis requires only prophylactic administration of narrow spectrum regimens active against aerobic and facultative and obligate anaerobes; treatment should be discontinued within 24 h
  - The administration of prophylactic antibiotics to patients with severe necrotizing pancreatitis prior to the diagnosis of infection is not recommended
- Additional comment on pharmacokinetic considerations[1]
  - Empiric therapy of patients with complicated intra-abdominal infection requires the use of antibiotics at optimal doses to ensure maximum efficacy and minimal toxicity and to reduce antimicrobial resistance

1 Solomkin J et al. Surgical Infection Society/IDSA. Clin Infect Dis. 2010;50:133-64.

# Skin and Soft-Tissue Infections Requiring Hospitalization: Opportunities for Antibiotic Stewardship

- Single institution academic medical center; 322 consecutive adult patients hospitalized during 2007 [1]
- Cellulitis, 20%; cutaneous abscess, 32%; SSTI with complicating factors, 48%
- Culture-positive results in 150 patients
  - 145 (97%) were *S. aureus* or streptococci
- Antibiotic selection and duration was excessive in culture-positive infections
  - Broad aerobic gram-negative activity, 61% - 80%
  - Anaerobic activity, 73% - 83%
  - Only one-third of patients received therapy targeted only at gram-positive organisms
  - Median duration of therapy was 13-14 days amongst 3 infection types
- Guideline implemented in 2009 led to several improvements: [2]
  - Microbiologic cultures decreased 80%
  - Median duration of therapy decreased from 13 days to 10 days
  - Decrease in use of broad aerobic gram-negative antibiotics (66% to 36%; P<0.001), antipseudomonal antibiotics (28% to 18%; P=0.02), or broad anaerobic activity (76% to 49%; P<0.001)

1 Jenkins T et al. Clin Infect Dis. 2010;51(8):895-903.
2 Jenkins T et al. Arch Int Med. 2011;171(12):1072-9.

# Optimizing Antibiotic Dosing Using Pharmacokinetic (PK) and Pharmacodynamic (PD) Principles

- FDA recommendations for antibiotic dosing in renal dysfunction are based on achieving similar AUC based on otherwise normal healthy volunteers of normal weight
  - Usually unpublished data (“on file”)
  - AUCs may not be an appropriate pharmacodynamic target
  - Since CrCL ranges can vary by 2- to 3-fold, beware of cutting doses in half
- FDA dosing recommendations are based on Cockcroft-Gault estimations (not on calculation of eGRF/MDRD) and use actual serum creatinine values
- Most FDA dosing recommendations are inaccurate in certain patient populations (obesity, low body weight, fluid overload, sepsis)
- Pharmacodynamics, as studied in hospitalized patients with infections, along with consideration of MICs, provides more accurate information on dosing antimicrobials
  - Once-daily dosing aminoglycosides
  - Prolonged infusion of short half-life (≤ 2 hrs) beta-lactams

# Pharmacodynamic Properties of Beta-Lactams That May Influence Clinical Success

- For beta-lactams, time free drug concentration is above MIC (fT>MIC) is the key pharmacodynamic variable
- Antimicrobial effect is estimated using % of dosing interval in which the free drug serum concentration exceeds the MIC (%fT > MIC)

| Percentage of the dosing interval required for the free drug concentrations that exceed the MIC of the pathogen for β-lactam antibiotics (% fTime > MIC) | | |
|---|---|---|
| Drug class | Stasis end point | Max kill end point* |
| Carbapenems | 20 | 40 |
| Penicillins | 30 | 50 |
| Cephalosporins | 40 | 60 - 70 |

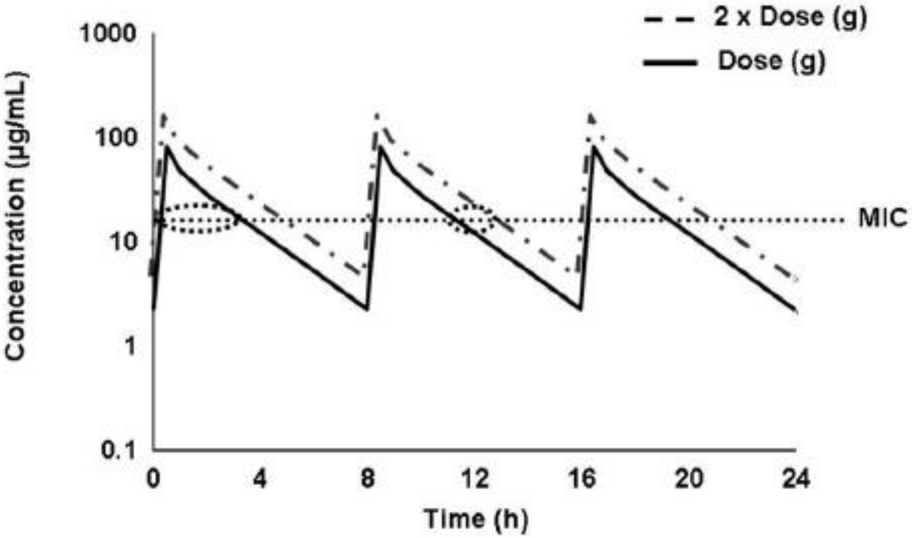
*Generally considered a 3- log reduction in colony forming units.

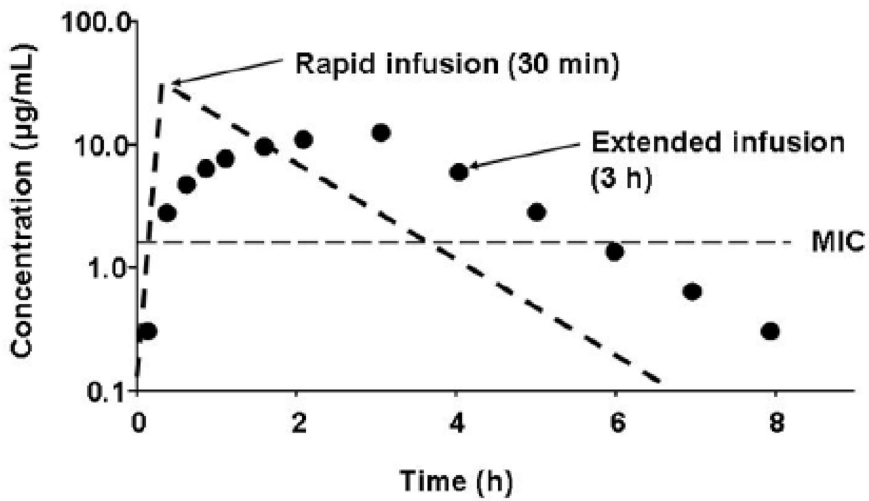
Drusano GL. Clin Infect Dis. 2003;36 (suppl 1):S42-50

# Prolonged Infusions of Beta-Lactams with Short Half-Lives Optimize PK-PD

- Dose escalation either by administering higher doses (or administering a dose more frequently; data not shown) achieves only small increments in efficacy because there is little increase in the time during which the drug concentration exceeds the MIC (fT>MIC)

- An extended infusion time for a carbapenem increases the time the drug concentration exceeds the MIC compared with a shorter infusion time




Nicolau D. Crit Care. 2008; 12 (suppl 4):1-5

# Optimizing Clinical Outcomes Using Prolonged Infusions of Beta-Lactams

- Single-center cohort study of patients who received piperacillin-tazobactam (PTZ) therapy for susceptible *P.aeruginosa* infection (n=194 patients)[1]
- Changed practice from intermittent infusions of PTZ (3.375 g IV for 30 min every 4-6 h) to extended infusions of PTZ (3.375 g intravenously for 4 h every 8 h)
  - Among patients with APACHE II scores ≥17, 14-day mortality rate was significantly lower among patients who received extended-infusion therapy than among patients who received intermittent-infusion therapy (12.2% vs. 31.6%, respectively; P=0.04)
  - Median duration of hospital stay after collection of samples for culture was significantly shorter for patients who received extended-infusion therapy than for patients who received intermittent-infusion therapy (21 days vs. 38 days; P=0.02).
- Using meropenem 2 gm Q8H or cefepime 2gm Q8H, both as 3-hr infusions, plus a clinical pathway, Nicasio et al demonstrated significant improvements in VAP patients[2,3]
  - Lower total costs associated with treatment of VAP and post-VAP hospitalization

1 Lodise TP  et al. Clin Infect Dis. 2007;44:357-63.
2 Nicasio A et al. J Crit Care. 2010;25:69-77.
3 Nicasio A et al. Pharmacother. 2010;30:453-62.

# ADDITIONAL SLIDES

# Hospitalized Patient Demographics: Potential Projects Focusing on Outcomes

- How frequently is metronidazole prescribed with pip/tazo, amp/sulb, carbapenems?
- Does the antibiogram eliminate duplicates?
- Is there an ability to classify isolates on the antibiogram as community-acquired vs hospital-acquired (i.e., present-on-admission)?
- Are you familiar with the medical staff’s understanding of antibiotics and their use?
- Do you know the contribution of HAIs to unexpected deaths in your institution?
- Do you know the cost associated with a 1% change in hand hygiene compliance?
- Is there data to account for non-compliance with JCAHO/CMS core measures for CAP?
- For patients with HAIs, what is the time to appropriate therapy?
- What is the frequency of prescribers stating an antibiotic plan in the chart?
- If MRSA screening is performed, how often is vancomycin prescribed following results?
- What is the prescriptive compliance for institutional guidelines regarding use of broad-spectrum beta-lactams?
- Have intensivists studied the duration of ventilator assistance in patients with VAP?
- For patients who are converted to PO antibiotics, what % are converted back to IV?
- Do you have data on % patients who receive antibiotics for > 3days?
- Have you tracked the rise of MDRO pathogens (e.g., ESKAPEs) in hospitalized patients?

# Prolonged Infusions of Beta-Lactam Antibiotics: Implications for Antimicrobial Stewardship[1]

- The optimal dosage and administration of antibiotics are essential to combat antibiotic resistance
- While many factors combine to play a role in favorable clinical outcomes, the absence of an appropriate dose and administration strategy of beta-lactams appropriate for the MIC of the pathogen, might lead to failure
- The literature contains many instances of “resistant pathogens” being successfully treated using prolonged infusions of higher dose regimens (but not necessarily “heroic” doses)
- Literature which suggests that clinical outcomes are not improved using prolonged infusions of beta-lactams often include the majority of infections due to pathogens with very low MICs, UTIs, and mild infections in non-immunocompromised patients
- Breakpoints have been lowered for many pathogens as a result of pharmacodynamics and target attainment
  - Piperacillin-tazobactam, *P.aeruginosa*
  - Carbapenems, Enterobacteriaceae (specifically to address KPCs)
  - Cephalosporins, ESBL-producing Enterobacteriaceae

1 George J, Towne T, Rodvold K. Pharmacotherapy. 2012;32(8):707-21.